REMARKS

Claims 1-13 are pending. Claim 4 is withdrawn. Claims 1, 3, and 8 are amended. Claim 14 is added. Accordingly, upon entry of the amendment, claims 1-14 will be pending.

The claims have been amended to claim more fully the recited subject matter and to make minor editorial changes. Support for the amendments can be found throughout the claims and specification as filed, and is discussed in more detail below. Specifically, support for the amendment of claim 8 and the addition of claim 14 may at least be found in the originally filed specification, for example, at page 13, lines 1-6. No new matter is added.

Amendment of the claims herein is not to be construed as acquiescence to any objections/rejections set forth in the instant Office Action and were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the subject matter of the claims as originally filed in this or one or more subsequent patent applications.

Claim Rejections – 35 U.S.C. §112

Claim 1 is rejected under 35 U.S.C §112, second paragraph, as allegedly indefinite for reciting "... fusion polypeptide bound to a carbohydrate on said antigen bearing target and includes said polypeptide which is not bound to said antigen bearing target...." Applicants respectfully disagree and traverse the rejection.

Without acquiescing to the reasoning underlying the rejection and in order to expedite prosecution, Applicants have amended claim 1 to recite "... fusion polypeptide bound to a carbohydrate on said antigen bearing target and includes said fusion polypeptide which is not bound to said antigen bearing target....." Support for the amendment is at least found in the specification as filed, for example, the paragraph spanning page 21, line 21 – page 22, line 2. Applicants respectfully submit it is clear that the composition includes fusion polypeptide which is not bound to the antigen

bearing target. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claim 3 is rejected under 35 U.S.C §112, second paragraph, as allegedly indefinite for reciting "vaccine." Without acquiescence and in order to expedite prosecution, Applicants have amended claim 3 to delete the recitation "vaccine." Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 8 is rejected under 35 U.S.C §112, second paragraph, as allegedly indefinite. The Office Action at page 4 alleges that claim 8 is unclear for reciting "wherein said cell is substantially unable to divide." Applicants respectfully disagree and traverse the rejection.

Without acquiescing to the reasoning underlying the rejection and in order to expedite prosecution, Applicants have amended claim 8 to recite "wherein said cell divides at a rate that is less than about 50% of the rate of division of corresponding cells which are not treated to prevent cell division." Support for the amendment is at least found in the specification as filed, for example, at page 13, lines 1-6. Applicants respectfully submit that the metes and bounds of claim 8 are clear. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Obviousness-type Double Patenting

The Office Action states that the instant claims are rejected under the judicially created doctrine of obviousness type double patenting in view of several co-pending applications. Upon notification of otherwise allowable subject matter in the instant case, Applicants will address the double patenting rejections.

Claim Rejections – 35 U.S.C. §103

Claims 1-3 and 5-13 are rejected under 35 U.S.C §103(b) in view of U.S. 5,891,432 to Hoo et al. ("Hoo") and Scholler et al. (J. Immunol. 2001; 166: 3865-3872; "Scholler"). Applicants respectfully disagree and traverse the rejection.

In order to make out a *prima facie* showing of obviousness, the Examiner must establish that there is some motivation in one or the other of the cited references or in the state of the art at the time the invention was made to combine the references, the combination of references must teach or suggest each and every element of the claimed invention, and there must be some reasonable expectation of success in making and using the invention. In addition, "[a] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.* 167 L. Ed. 2d 705, 712. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)).

The presently claimed invention is a composition suitable for administration to a subject, said composition comprising an antigen bearing target and a fusion polypeptide, said fusion polypeptide comprising a first amino acid sequence which can bind to a carbohydrate and a second amino acid sequence comprising a ligand for a cell surface polypeptide of a leukocyte, wherein said composition includes said fusion polypeptide bound to a carbohydrate on said antigen bearing target and includes said fusion polypeptide which is not bound to said antigen bearing target.

Applicants have discovered that compositions comprising bound and free fusion polypeptide, where the bound fusion polypeptide is bound to a carbohydrate on the cell by a cell—surface binding moiety, are effective for modulating an immune response. This is at least shown in the specification at Example 18, in which administering melanoma cells and fusion protein (GM-CSF-HA1) reduced the number of metastases in a mouse model about 10-20 fold as compared to mice administered with melanoma cells and GM-CSF. In Example 19, there was an increased number of tumor-free mice that were administered melanoma cells and fusion protein (GM-CSF-HA1) (7 of 10) compared to mice administered melanoma cells and GM-CSF (1 of 5). Applicants were the first to appreciate that administering a composition of the invention containing <u>both</u>

fusion protein bound to cells by a carbohydrate (e.g., sialic acid) and unbound fusion protein (i.e., free fusion polypeptide) was effective in vaccinating mice against tumor development. Thus, the presently claimed invention is based, at least in part, on these discoveries.

In contrast, Hoo fails to teach or suggest such a fusion protein that is bound to a carbohydrate of a cell. As acknowledged by the Examiner on page 8 of the Office Action, "Hoo does not specifically teach the binding of the fusion polypeptide via a carbohydrate on a cell through a first amino acid sequence that can bind to sialic acids on a glycoprotein or a sequence that comprises a carbohydrate binding domain of a naturally occurring lectin." The Examiner has further cited Scholler as an alleged remedy for the deficiencies of Hoo. However, the Examiner's reliance on Scholler is misplaced.

Applicants respectfully submit that there is no motivation to combine Scholler and Hoo in the manner proffered by the Examiner to arrive at Applicants' claimed composition.

1) There is no motivation to combine Hoo with Scholler because Hoo does not teach using CD antigens that are not integral membrane proteins

In support of the rejection, the Examiner at page 9 of the Office Action: "One would have been motivated to [modify the composition taught by Hoo], given the suggestion by Hoo that the cell-binding moieties be used to associate a fusion polypeptide with a membrane of a cell, such as using CD antigens as the attachment factor."

Applicants respectfully disagree. Instead, Hoo clearly states at column 7, lines 32-37: "Membrane attachment domains useful in the invention also can be derived from cell adhesion molecules such as cadherins, integrins, selectins and members of the immunoglobulin superfamily; ***as well as other integral membrane proteins such as CD antigens.***" (emphasis added).

In the context of Hoo, the CD antigens used to attach a fusion protein to the cell membrane are **integral membrane proteins**. Hoo does not teach or suggest a CD

antigen that binds a carbohydrate, or even using a CD antigen that binds a carbohydrate as a membrane attachment domain.

The CD83 antigen taught by Scholler binds a carbohydrate, in contrast to the CD antigens taught by Hoo, which are integral membrane proteins. Thus, one would not be motivated to combine Scholler with Hoo, which does not teach CD antigens that are not integral membrane proteins.

2) There is no motivation to combine Scholler with Hoo because Scholler does not teach a ligand for a cell surface polypeptide of a leukocyte.

Likewise, there is no motivation to combine Scholler with Hoo. As acknowledged on page 8 of the Office Action, Scholler teaches a "CD83 molecule fused to a mutated Ig constant region." However, Scholler does not teach or suggest attaching a CD83 molecule to a **ligand for a cell surface polypeptide of a leukocyte**, as recited in the claims.

Instead, in the CD83Ig fusion protein constructed by Scholler, the human IgG1 constant region was mutated to **eliminate** its binding activity: "These structural modifications eliminated the binding to FcR [Fc receptor]." (page 3867, 1st full paragraph). Thus, the mutated IgG1 constant region of Scholler is unable to function as a ligand (e.g., for a cell surface polypeptide of a leukocyte).

As Scholler teaches eliminating Fc receptor binding in human IgG1 constant region, Scholler teaches away from fusing CD83 to a polypeptide that is a ligand for a cell surface polypeptide. Based on Scholler, one would not have been motivated to fuse CD83 to a ligand for an Fc receptor or a ligand for a cell surface polypeptide of a leukocyte. Thus, Applicants respectfully submit that one would not have been motivated to combine Hoo with Scholler, which teaches away from fusing CD83 to a ligand for a cell surface polypeptide.

3) There is no motivation to combine Scholler with Hoo because Hoo teaches that the fusion protein is a non-antibody immunomodulatory molecule.

Hoo teaches a cellular vaccine having a membrane-bound fusion protein that includes a non-antibody immunostimulatory molecule such as GM-CSF (Abstract). Hoo is clear that the membrane-bound fusion proteins do not include an antibody component.

In contrast, Scholler teaches fusion of a CD83 molecule to a mutated human **IgG1 constant region** (Abstract). This conflicts with the teachings of Hoo, which repeatedly states that their membrane-bound fusion proteins are **non-antibody** immunomodulatory molecules (see, e.g., Abstract, Summary of the Invention, Detailed Description of the Invention). Accordingly, one would not be motivated to combine Hoo with Scholler, which teaches fusing CD83 and an antibody fragment (i.e., IgG1 Fc).

Thus, at the time the invention was made, one of skill in the art would lack the motivation or expectation of success to generate the fusion polypeptides of Applicants' invention based on Hoo and Scholler.

4) Hoo and Scholler do not teach a composition comprising bound and unbound fusion protein.

Even so, Applicants respectfully submit that Hoo and Scholler either alone or in combination, do not teach or suggest the element "wherein said composition includes said fusion polypeptide bound to a carbohydrate on said antigen bearing target and includes said fusion polypeptide which is not bound to said antigen bearing target," as required by instant claim 1 and dependent claims thereof. As set forth above, Applicants have amended claim 1 to recite that the composition includes said fusion polypeptide which is not bound to the antigen bearing target.

The Examiner at page 7 of the Office Action has cited column 18, lines 33-62 of Hoo in support of the rejection. However, this section of Hoo does not teach or suggest a composition comprising both bound and unbound fusion polypeptide. At best, Hoo teaches that a vaccine of the invention can comprise a second immunomodulatory

molecule in membrane-bound or soluble form (column 18, lines 33-51). In this regard, Hoo teaches combinations of distinct cytokines (e.g., preferably GM-CSF and IL-4 at column 18, lines 53-62), but does not teach that a cytokine is present in both membrane-bound and soluble form. Moreover, Hoo does not teach that the cytokine in soluble form is fused to a membrane attachment domain as a fusion protein. In contrast, the currently amended claims require both **bound and unbound fusion polypeptide** (e.g., bound GM-CSF-HA and GM-CSF-HA).

In sum, there is nothing in either of the cited references or in the state of the art at the time the invention was made that provides one of ordinary skill in the art with motivation to combine the references in the manner proffered by the Examiner. Assuming *arguendo* that there were such motivation, which there is not, the combination does not teach or suggest each and every element of the claimed invention because neither reference teaches or suggests **bound and unbound fusion protein** as recited in the instant claims. Therefore, because the cited combination of references does not put one of ordinary skill in the art in possession of the claimed invention, one of ordinary skill in the art would not have a reasonable expectation of success in making and using the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and arguments, Applicants respectfully request reconsideration and withdrawal of all pending objections/rejections and allowance of the applications with claims 1-3 and 5-12 presented herein. If a telephone call with Applicants' representative would be helpful in expediting prosecution of the application, Applicants invite the Examiner to contact the undersigned at the telephone number shown below.

Applicants submit this paper in response to the office action dated March 11, 2011. Applicants believe that no fees are required for consideration and entry of this paper. Nevertheless, Applicants hereby authorize the Director to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. **04-1105**, under Order No. 85849DIV4(211111).

Dated: June 11, 2011

Respectfully submitted,

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